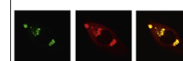


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## Research Report

# Module number of default mode network: Inter-subject variability and effects of sleep deprivation

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## ABSTRACT

Sleep deprivation have shown its great influence on the default mode network (DMN). The DMN is a core system in resting state brain activity. Recent studies have focused on its subsystems and multiple functions. However, the individual specific organization of the DMN is rarely investigated. As the effects of sleep deprivation (SD) on mood are well documented, a more interesting question is whether changes in the processing of emotional information due to sleep deprivation are related to any specific topological properties of the DMN. In this study, we proposed an index, module number of DMN (mnDMN), to measure the specific modular structure of the DMN for each individual. Our results showed that the DMN was generally split into two modules after SD, and the decreased functional connectivity between the two modules was related to a worsening of the participants' self-reported emotional state. Furthermore, the mnDMN was correlated with participants' rating scores of high valence pictures in the SD session, indicating that the mnDMN might reflect mood valuation in the human brain. Overall, our research reveals the diversity of the DMN, and may contribute towards a better understanding of the properties and functions of the DMN.

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## 1. Introduction

The default mode network (DMN) is possibly the most widely studied functional network in resting-state functional Magnetic Resonance Imaging (rsfMRI) literature (Lei et al., 2013b). Recent research has focused on its subsystems and multiple functions during various experimental conditions (Alex

Fornito et al., 2012) and mental disorders (Zhang and Raichle, 2010). Though the existing literature has indicated that the DMN consists of approximately 10 widely reported regions (Andrews-Hanna et al., 2007; Hayes et al., 2012), the medial prefrontal cortex (mPFC) and the posterior cingulate cortex (PCC) constitute a midline core subsystem of the DMN (Greicius et al., 2003; Sheline et al., 2009). The decreased

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activity of the PCC often serves an adaptive function and is implicated in transitions between focusing on external and internal environments (Eichele et al., 2008; Raichle et al., 2001). However, Leech and Sharp recently pointed out this region was proved to be highly heterogeneous and might contribute a lot in regulating the focus of attention (Leech and Sharp, 2013). In contrast, the mPFC has been associated with social cognition involving the monitoring of one's own psychological states, and mentalizing about the psychological states of others (Laird et al., 2009; Lei et al., 2013, 2014).

Recent evidence suggested that the DMN is generally made up of three subsystems including the aforementioned midline core subsystem, as well as the dorsal medial pre-frontal cortex subsystem and the medial temporal lobe subsystem (Andrews-Hanna et al., 2007; Salomon et al., 2013). However, the reproducibility of this compartmentalization needs to be further tested based on the following recent findings. Andrews-Hanna, the proposer of these three subsystems, has found that an inconsistency exists in the DMN structure between the rest and task conditions by using clustering coefficient analysis (Andrews-Hanna et al., 2010). Besides, by using meta-analysis, Kim found a so-called “parietal-temporal subsystem”, which partially overlapped with the medial temporal lobe subsystem (Kim, 2012). Furthermore, substantial evidence indicated that nodes in the same subsystem are heterogeneous. For instance, aging has differential effects on the activity of the mPFC and the PCC, and thus causes reduced functional connectivity between them (Andrews-Hanna et al., 2007). Another example comes from the research of sleep, which suggests that the bilateral inferior parietal cortices and the PCC strengthen their activity during deep sleep, whereas the connections between the PCC and the mPFC are lost (Horowitz et al., 2009). Given the controversy, regarding the subsystem organization of the DMN, we hypothesized that the DMN structure is very diverse and consequently a quantitative tool should be developed in order to capture the heterogeneity of the DMN.

Modularity is a popular network measurement to quantify functional segregation in the brain (Liang et al., 2013). The network's modular structure, also known as the community structure, is revealed by subdividing the network into groups of nodes, with a maximum possible number of within-group links, and minimal between-group links (Girvan and Newman, 2002). Two particularly informative early studies were conducted exploring brain network modularity, supporting a substantial correspondence between structural connectivity and resting-state functional connectivity measured in the same participants (Chen et al., 2008; Hagmann et al., 2008). By using modularity, functional brain networks

such as sensory-motor, visual, and mnemonic processing networks are easier to locate in terms of their corresponding topological modules. It is important to note that the DMN was proved to have an intrinsically cohesive modular structure (He et al., 2009). Most importantly, the characteristics among modules provide important means for identifying individual differences in network organization (Sporns, 2013), and help us to identify groups of regions that perform specific biological functions. However, the individual module structure of the DMN remains largely unknown.

In the present study, sleep deprivation (SD) was utilized to investigate the specific organization of the DMN in each individual. SD was chosen because previous studies have shown its great influence on the DMN. Given De Havas et al.'s (2012) finding that the functional connectivity between regions within the DMN was found to decrease after SD, we were interested to confirm the existence of functional segmentation in the DMN module structure. Moreover, although the DMN is typically reported as being anti-correlated with the dorsal attention network (DAN), different relationships have been observed when considering specific subsystems of the DMN, which further indicates functional segmentation of the DMN (Broyd et al., 2009). Two other interesting phenomena are the disturbed mood state after insufficient sleep (Zohar et al., 2005) and that sleep loss usually interacts with emotion disturbance, such that nearly all psychiatric and neurological disorders expressing sleep disruption display corresponding symptoms of affective imbalance (Benca et al., 1992). As DMN alterations have been reported in numerous neuropsychiatric diseases (Zhang and Raichle, 2010), a relevant question is whether changes in the processing of emotional information due to sleep deprivation are related to any specific topological properties of the DMN.

According to the above research evidence, we hypothesized that the principle of modularity would characterize the fundamental organization of the default mode network under a sleep deprivation condition. This study had three main objectives. Firstly, to investigate the effect of sleep deprivation on the DMN, a metric named ‘module number of DMN’ (mnDMN) was proposed to compare the individual modular structure of the DMN between normal sleep (NS) and sleep deprivation conditions of 22 healthy subjects. Secondly, we wanted to see whether functional segmentation exists in the DMN module structure, in other words, whether the DMN would split into more modules in the SD condition by using a method of averaging the functional connectivity across participants (the grand averaged functional connectivity). So mnDMN refers to the individual level of modularity analysis while the grand averaged functional connectivity is group

**Table 1 – Sleepiness, mood state and rating scores of subjects in both NS and SD sessions.**

Behavior performance	NS session	SD session	p
Sleepiness	2.36±0.85	3.14±1.13	<0.001
Positive affect	33.64±4.34	28.05±6.22	<0.001
Negative affect	17.45±5.54	17.23±6.1	0.0804
Negative picture rating scores	3.63±0.42	3.48±0.49	0.12
Positive picture rating scores	3.23±0.52	3.12±0.45	0.2
High valence picture rating scores	3.43±0.43	3.3±0.45	0.11

level modularity analysis. Finally, taking into account the perplexing emotional reactivity people demonstrate after sleep deprivation, we further explored the relationship of the individual module number of the DMN and participants' ratings of high valence pictures.

## 2. Results

### 2.1. Behavior results

Sleep deprivation resulted in an increase in the sleepiness of participants (2.36 vs. 3.14;  $t_{21}=2.08$ , paired t-test,  $p<0.001$ ; Table 1). At the same time, there was a significant reduction in their positive affect (33.64 vs. 28.05;  $t_{21}=2.08$ , paired t-test,  $p<0.001$ ; Table 1). To indicate that participants indeed have made a choice rather than no response during the emotional rating task, we further reported the percentage responses at each valence both in the NS and SD sessions in Fig. 1. We noticed that the choice of 3 and 4 are relatively more than the choice of 1, 2 and 5. However, their negative affect and emotional rating scores of negative pictures, positive pictures as well as high valence pictures were not significantly different across conditions ( $p=0.0804$ ,  $p=0.12$ ,  $p=0.2$ , and  $p=0.11$ , respectively; Table 1).

### 2.2. The extracted DMN

According to the results of group independent component analysis (GIFT, <http://www.icatb.sourceforge.net/>) (Calhoun et al., 2001), the default mode network was identified with a 0.47 spatial correlation value with the Stanford University template. Its spatial distributions are shown in Fig. 2 (upper left). Paired t-tests at the group level of each network revealed no areas which were significantly changed between NS and SD sessions ( $p<0.01$ ). The DMN encompassed the medial prefrontal cortex, bilateral temporal lobe, bilateral angular cortex, precuneus, posterior cingulate cortex, and bilateral cerebellum, which are illustrated in the bottom left of Fig. 2. The specific positions of 13 single spherical regions which

were entries for mnDMN analysis are listed in the right table of Fig. 2.

### 2.3. Sleep deprivation reconfigures functional networks

According to our results of modularity analysis, the DMN split into two modules with one consisting of 7 regions and another consisting of 6 regions in the SD session compared to the NS session, which is shown in both sides of Fig. 3. The anterior subsystem of the DMN (DMN1) encompassed the medial prefrontal cortex, left medial superior frontal area, left inferior orbital frontal cortex, left middle temporal area and bilateral cerebellum. The posterior subsystem of the DMN (DMN2) encompassed the bilateral angular cortex, bilateral temporal lobe, precuneus, posterior cingulate cortex and inferior temporal area. We then examined the functional interaction between modules. Paired t-tests between correlations in the NS and SD sessions indicated a significant decrease (in the middle of Fig. 3) from 0.35 to 0.24, DMN1 and DMN2 functional connectivity ( $p=0.036$ ).

Furthermore, we used Pearson correlations to investigate whether the individual functional connectivity between DMN1 and DMN2 was able to predict individual differences in the rating of mood. As shown in Fig. 4, participants with more reduced DMN1-DMN2 connectivity were found to have a much worse emotional state in the SD session ( $r=-0.58$ ,  $p=0.0047<0.01$ ).

### 2.4. MnDMN correlates significantly with participants' performance

The split DMN in the group average connectivity matrix further investigates how the modularization of the DMN varies across subjects. As illustrated in Fig. 5, 22 subjects were sorted by the number of modules, i.e., mnDMN. From left to right, the color increases from white to deeper green to reflect that the mnDMN increased from 2 to 5.

The relationship between participants' rating scores of high valence pictures and mnDMN was examined in the SD session, which is specifically shown in Fig. 6. From this, we can identify that the more modules the DMN splits into, the higher the participant's ratings of emotive pictures. For instance, the subject whose DMN corresponds to two modules in the SD session, has a rating score of 2.85 (black circle dotted in Fig. 6), whereas the other subject with a rating score of 3.33, had a DMN which split into 3 modules in the SD session (yellow circle dotted in Fig. 6). The subject whose DMN divided into 4 modules in the SD session had a much higher rating score equal to 3.63 (blue circle dotted in Fig. 6) and the most extreme division of the DMN was observed in the subject whose rating score was 3.88, with his DMN transformed into 5 modules in the SD session (green circle dotted in Fig. 6). We further used Pearson correlations to test whether individual modularity of the DMN in the SD session could predict participants' ratings. As illustrated in Fig. 6, we found individual's DMN modularity was positively correlated with emotional rating scores to high valence pictures in the SD session ( $r=0.53$ ,  $p<0.01$ ).

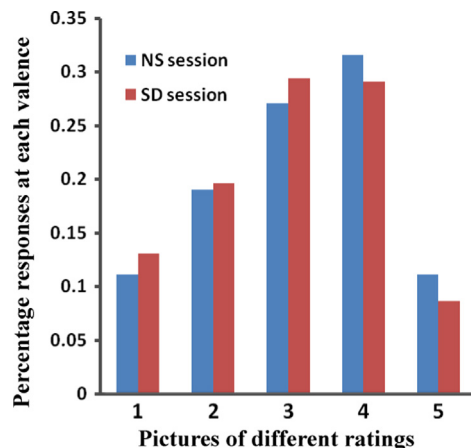
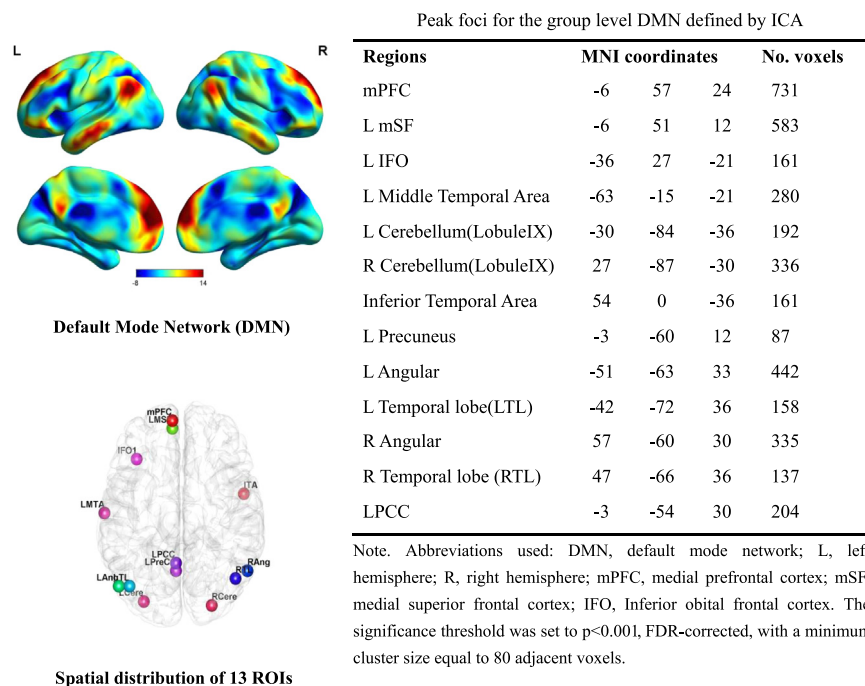
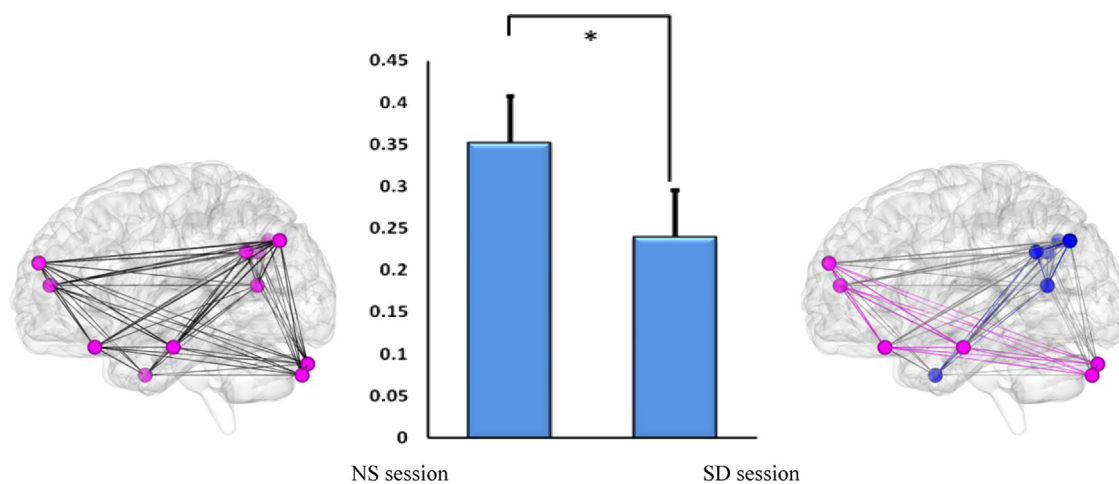


Fig. 1 – The percentage responses at different emotional ratings in the NS (indicated by blue rectangle) and SD (indicated by red rectangle) sessions.



**Fig. 2 – The spatial pattern of the DMN and its 13 regions of interest (ROIs).** The positive and negative activation of group level DMN extracted by ICA is shown in the upper left. The localizations of 13 ROIs are displayed in the bottom left. Each color represents a single ROI in axial view. The 13 ROIs were mapped on the cortical surfaces using BrainNet viewer software (<http://www.nitrc.org/projects/bnv/>). The specific positions of 13 ROIs are illustrated in the right table.



**Fig. 3 – DMN split into two sub-networks after sleep deprivation.** The middle panel shows the functional connectivity between DMN1 and DMN2 during NS and SD sessions, with the corresponding spatial patterns in the left and right panels. In the NS session, there is only one module (all nodes are plotted in magenta, all the edges are plotted in black). In contrast, there are two modules in the SD session, the anterior DMN (magenta regions and edges) and the posterior DMN (blue regions and edges), and the edges between the two modules are black. The nodes and connections were mapped on the cortical surface using BrainNet viewer software (<http://www.nitrc.org/projects/bnv/>).

### 3. Discussion

In the present study, we found SD induced the DMN splitting into two modules and reduced the interaction between modules across subjects on the group level of modularity analysis, which suggested functional segmentation existed in the DMN module structure. The decreased functional

connectivity between modules was negatively correlated with the change in participants' rating of their negative mood. To quantitatively describe the influence of SD, we proposed an index, the module number of DMN (mnDMN), to measure the inter-subject variability in the structure of the DMN. Our data suggested the mnDMN in SD sessions was



correlated with participants' rating scores of high valence pictures in SD sessions on the individual level of modularity analysis, which uncovered SD effects on the interaction between DMN organization and the mood variation of participants.

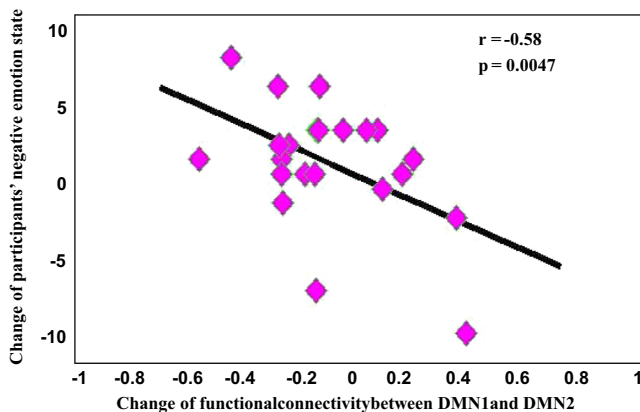
### 3.1. Sleep deprivation reconfigures default mode network

Altered functional connectivity within the DMN was observed with increased subsystems corresponding to DMN1 and DMN2. As illustrated in Fig. 3, DMN1 mainly encompassed the mPFC and bilateral cerebellum and DMN2 consisted of the bilateral parietal lobule and bilateral temporal lobes as well as the PCC. Though rarely reported in previous literature, our findings linking the bilateral cerebellum to the DMN are supported by some related research (Filippini et al., 2009; Habas et al., 2009). Moreover, the cerebellum is involved in past and future event elaboration in conjunction with the mPFC (Addis et al., 2007). The latter reflects the neural substrates of some components of social cognition (Buckner

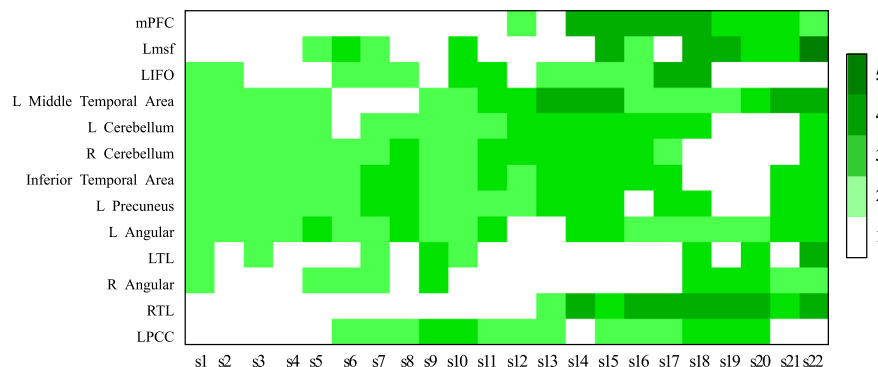
et al., 2008). Therefore we deduced that DMN1 is mainly responsible for monitoring of one's own psychological states and social cognitions. Correspondingly, the PCC, part of DMN2, supports transitions between external and internal environments (Leech and Sharp, 2013). Meanwhile the bilateral parietal lobule and bilateral temporal lobes were proved to constitute a medial temporal lobe sub-system and mainly support memory retrieval processes (Andrews-Hanna et al., 2010; Kim, 2012). Hence DMN2 supports the cognition of not engaging in the external environment. In conclusion, our results suggest modularity is a promising tool to identify functional subsystems of the DMN.

Compared with normal sleep, a significantly decreased functional connectivity between DMN1 and DMN2 was observed in sleep deprivation. Basically, the altered integrity within the DMN supports previously reported aberrant functional connectivity between the anterior and posterior components of the DMN under a wide range of experimental conditions, such as deep sleep (Horowitz et al., 2009) and working memory tasks (Castellanos et al., 2008). Moreover, as Broyd and his colleague pointed out in their review, the reduced anti-correlations may arise from the abnormal DMN activity (Broyd et al., 2009). We also observed the decreased DMN-DAN anti-correlation (from  $-0.4337$  to  $-0.2442$ ,  $p=0.0014$ ), which may partially be attributed to the decreased DMN1-DMN2 functional connectivity.

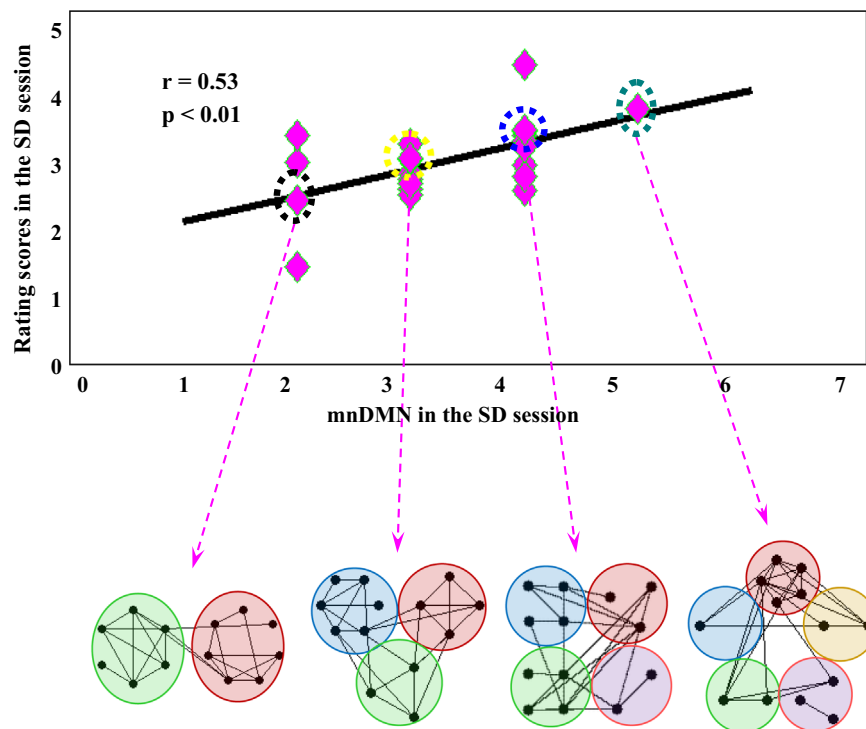
Interestingly, significantly decreased DMN1-DMN2 functional connectivity was found to be negatively correlated with participants' negative emotional state in our study. This relationship demonstrates participants would have a much worse mood after SD. Our result therefore provides additional evidence about the role of the DMN in emotion regulation. Furthermore, given that decreased connectivity between the anterior and posterior components of the DMN has been shown to underlie deficits in self-referential processing, attention control and working memory (Castellanos et al., 2008; Sheline et al., 2009), it is not surprising to find that SD also bring about decreased connectivity between these two components. In fact, many previous studies have reported the negative effects of SD (Zohar et al., 2005). This further illustrates that functional segregation of the DMN may serve to worsen emotion state, though participants did not report



**Fig. 4 – The functional connectivity between DMN1 and DMN2 and its relationship with participants' state of mood.** Participants who have more decreased functional connectivity between DMN1 and DMN2 were found to have a worse mood in the SD session compared to NS session ( $r = -0.58$ ,  $p = 0.0047 < 0.01$ ). Each magenta diamond represents a single subject.



**Fig. 5 – The modularity of 13 DMN regions across 22 subjects in the SD session.** The Y axis is labeled with 13 regions of the DMN, and the X axis is labeled with 22 participants. Notably, the number of DMN modules (mnDMN) is increased from 2 to 5. The deeper color for the latter subject (especially s22) represent that they required more modules during rest state.



**Fig. 6 – Module number of DMN (mnDMN) was correlated with participants' behavior performance during SD session. A positive correlation was obtained between mnDMN and the emotional rating scores of high valence pictures ( $r=0.53$ ,  $p=0.01$ ). Each magenta diamond represents a single subject. We chose 4 subjects, whose mnDMN corresponded to 2, 3, 4 and 5 along the fitted line, to illustrate their module structure in the bottom. Note only the largest 30% of links were shown in each network.**

worse mood in our behavior results (note the marginally decreased value in Table 1, though it was not-significant).

### 3.2. MnDMN is correlated with behavior performance

Although by utilizing the modularity analysis, we found the DMN split into two subsystems at the group level, this finding was constrained by our special experimental condition, sleep deprivation. As mentioned in our review of the previous research about subsystems of the DMN, some researchers have attempted to distinguish that some of the nodes belong to a specific module. As a result, it was clear that the division of the DMN subsystems couldn't obtain a unified result, because the function and the underlying structure of each node in the DMN may alter in different experimental conditions, different consciousness levels and different participants. In addition, clustering a specific node to a module is sensitive to the noises and nuisance variances related to the node. We consequently decided against attempting to subdivide the DMN according to specific groups with certain nodes. Since the module number could reflect the dynamic change of the default mode network in different situations (Tagliazucchi et al., 2013), we adopted a more summarized index, the mnDMN, which reflects the module number of the DMN, to abstractly describe the diversity of the DMN. What's more, the mnDMN only considers the number of modules rather than the specific composition within modules, thus it can be easily computed and more robust. We should

emphasize that the mnDMN is specially defined to describe the individual specific properties of the DMN. Our present study revealed its relevance to worse emotional states during sleep deprivation.

In our study, the individual mnDMN was correlated to subjects' rating scores of high valence pictures. Most pertinent to this finding, recent evidence suggests that other measures of inter-subjective variability of modularity can characterize other areas of participants' behavioral performance such as working memory and skill learning (Bassett et al., 2011; Stevens et al., 2012). Using a simple motor learning task, Bassett et al. found the allegiance of nodes to modules in each participant could be used to predict that participants' learning in a following experimental session (Bassett et al., 2011). Later on, Stevens et al. found another property of module networks: the modularity value that reflects how well an entire network is organized into modules can predict the change in working memory capacity. This further suggested organizational characteristics of module structures contain information about latent cognitive functions (Stevens et al., 2012). Combined with these two studies, our results intuitively suggest the importance of quantifying the module structure of the DMN in order to understand the emotional function of DMN. Future investigations should reveal the relationship among the allegiance of nodes to modules, the modularity value and mnDMN.

Participants with more subsystems of the DMN reported higher rating scores of high valence pictures in the SD session (see Fig. 6). This behavior performance was to be expected as

previous research has established that participants provide exaggerated rating of emotional materials after SD (Gujar et al., 2011; Kahn-Greene et al., 2006). Combined with the above result of decreased DMN1–DMN2 integrity after SD, an intuitive inference is that there is a linear relationship between the ratings of emotional pictures and the module number of DMN. What's more, this relationship is also relevant to a number of the aforementioned psychiatric disorders. These disorders are usually characterized by a deficit in emotional processing (Harrison et al., 2008) and a dysfunction in the DMN (Broyd et al., 2009). In fact, Gujar has suggested an interaction between sleep deprivation, emotion and mental disease in anxiety disorders (Goldstein et al., 2013). The increased module number of DMN may quantify this dysfunction, and further predict the deficit in emotional processing. Future application of mnDMN in mental disease may extend our knowledge of the underlying psychopathology mechanism of neuropsychiatric disorders.

### 3.3. Limitation

It should be noted that this study has some limitations. First, there is a lack of an objective monitoring of sleep, which is a flaw of our experimental design. Simultaneous EEG or other means during the resting state scan is a better way to confirm participants' wakefulness. Future sleep deprivation related studies should pay attention to the objective monitoring of sleep. Second, participants could only give their ratings by a moving cursor during the emotional rating task, which might make them less willing to move the cursor multiple steps, especially after sleep deprivation. A better and easier way to collect participants' ratings of emotional pictures will be needed in future studies. Third, nuisance variables in the BOLD signal, containing the mean signals from a ventricular region, the white matter region, the cerebrospinal fluid and the global brain signal were not removed in our modularity analysis. One consideration is that regressing out those covariates in the research area of brain functional connectivity is controversial (Murphy et al., 2009; Nair et al., 2014); another consideration is that nuisance variables might be affected by SD in sleep deprivation studies (Gujar et al., 2010, 2011), so nuisance variables might be related to participants' emotional experience in our SD paradigm. However, for the sake of caution, all data were reanalyzed after regressing out the nuisance effects. There were some minor changes with the correlation between mnDMN and participants' rating scores to high valence pictures in SD session. The correlation after moving out nuisance variables is 0.38 ( $p=0.08$ , that is marginally significant). Though this minor change may be caused by nuisance variables, the whole trends remained.

## 4. Conclusions

In summary, we have investigated the functional segregation and diversity of the default mode network in sleep deprivation using modular analysis. Sleep deprivation induced the DMN splitting into two subsystems, DMN1 and DMN2. The decreased connectivity of these two subsystems was negatively correlated with participants' emotional state. Most importantly, the module number of DMN (mnDMN) was

correlated with subjects' evaluations of emotive pictures in a sleep deprived state. Overall, the proposed mnDMN may be a useful index to depict the diversity of the DMN and its inter-subject variability, and enable other researchers to further explore the role of the DMN in related neuropsychiatric diseases.

## 5. Materials and methods

### 5.1. Participants

Twenty-three healthy right-handed volunteers participated in the experiment after giving informed consent. They were without any history of psychiatric or neurological illness as confirmed by a psychiatric clinical assessment. All had normal or corrected to normal vision. All of them had a good sleep habit and a normal sleep-wake rhythm with sleep duration of no less than 7 h each night in the past one month according to the Pittsburgh Sleep Quality Index (PSQI). Subjects abstained from caffeine and alcohol for 72 h prior to and during the entire course of the study. The study was approved by the Ethics Committee of Southwest University, and all procedures involved were in accordance with the sixth revision of the Declaration of Helsinki. One participant was excluded in our data analysis due to his fallen asleep in the scanner after sleep deprivation when he was performing the emotional rating task, then 22 participants (13 males, age:  $21.09 \pm 1.95$ ) were remained for our further analysis.

### 5.2. Study procedure

All volunteers visited the laboratory at Southwest University 3 times. During their first visit, they were informed of the whole study procedure, and completed questionnaires about their mental health and sleep habits. Then they were asked to adhere to their normal sleep habit until the end of the experiment, which was verified by a sleep diary. All of the participants needed to keep a sleep diary beginning one week before the formal experiment. This enabled volunteers to form a psychological contract relationship with our experiment. Volunteers returned to the laboratory weekly for two fMRI scan sessions, one after normal sleep (NS session) and one after sleep deprivation (SD session). The order of the two sessions was counterbalanced across participants.

Volunteers got up in the morning as usual on the day of their sessions. For the NS session, scans took place at 15:00 p.m. For the SD session, participants were monitored in the lab from 8:00 a.m. on Day 1 until 17:00 p.m. on Day 2 to ensure approximately 33.54 h ( $\pm 2.5$ ) total sleep deprivation before scanning. They were allowed only to engage in non-strenuous activities such as reading and watching videos. What's more, we have arranged a few experimenters to take turns to vigil in the lab. These strategies were useful to make sure the participants stay awake before their resting state scan. Volunteers had the right to quit the experiment at any time if they felt uncomfortable. Volunteers were asked to complete the Stanford Sleepiness Questionnaire (SPQ; Hoddes et al., 1972) and the Positive and Negative Affect Scale (PANAS; Watson et al., 1988) to estimate their state of

consciousness and mood before two fMRI scans. After a 5 min resting-state fMRI scan, they continued to perform an emotional picture rating experiment in the scanner (van der Helm et al., 2011), which contains 5 runs with a duration of 4 min 30 s in each run.

During the emotional rating task, participants viewed and rated the emotional intensity of 150 standardized affective pictures (International Affective Pictures System, IAPS, valence  $8.19 \pm 1.66$ , mean and std:  $4.98 \pm 1.38$ , arousal  $6.99 \pm 2.6$ , mean and std:  $4.99 \pm 1.1$ ) on a scale from 1 to 5, corresponding to the increasing intensity of their subjective emotional reaction to the pictures. Each event-related trial began with a fixation cross (500–1000 ms jittered), followed by a picture stimulus presentation (2000 ms). Participants rated the emotional intensity of the stimulus by a moving cursor. At the beginning of each trial, the cursor was stayed at the rating score of “3”. Since participants may move the cursor multiple steps to the target score, we couldn't collect their reaction time when they were rating the pictures. In extreme case, the participants may give no response if their target was “3”. Each trial was completed by a 2000–2500 ms fixation (jittered). The average rating scores of negative and positive pictures in both sessions were calculated respectively. We also calculated the participants' rating scores of high valence emotional pictures (according to the standard valence scores in the IAPS).

To ensure that participants stay awake in the scanner, they were instructed to stay awake and avoid sleeping. Participants were immediately addressed after each fMRI run via the intercom to ensure they stay awake and not to move their head. If a participant fallen asleep in the scanner, he/she couldn't hear our voice through the intercom. All the remained 22 participants answered us immediately after each run. After the complete fMRI scan, we further required participants to accomplish a Flanker task. According to our behavior analysis, though sleep deprivation resulted in an decrease in the congruency effect of participants (0.34 vs. 0.30;  $t_{21}=2.08$ , paired t-test,  $p<0.05$ ), it didn't affect participants' reaction time (267.81 vs. 266.41;  $t_{21}=2.08$ , paired t-test,  $p>0.05$ ) and accuracy rate (0.97 vs. 0.97;  $t_{21}=2.08$ , paired t-test,  $p>0.05$ ). Thus the alertness of participants didn't affected by sleep deprivation, which further indicated that they could be able to stay awake in the scanner.

### 5.3. fMRI scan and data recording

A high-resolution T1-weighted structural volume was acquired using a 3T Siemens Trio scanner. The 3D spoiled gradient recalled (SPGR) sequence used the following parameters: thickness of 1 mm (no gap); TR of 8.5 ms; TE of 3.4 ms; FOV of  $240 \times 240 \text{ mm}^2$ ; flip angle of  $12^\circ$ ; and a matrix of  $512 \times 512$ . The high-resolution T1-weighted structural volume provided an anatomical reference for the functional scan. Subsequently, the fMRI machine scanned 200 functional volumes, using an EPI sequence with the following parameters: TR of 1500 ms; TE of 29 ms; flip angle of  $90^\circ$ ; acquisition matrix of  $64 \times 64$ ; in-plane resolution of  $3.0 \times 3.0 \text{ mm}^2$ ; FOV of  $192 \times 192 \text{ mm}^2$ ; axial slices of 25; thickness/gap of 5/0.5 mm. The first six volumes were discarded to ensure steady-state longitudinal magnetization.

### 5.4. fMRI data pre-processing and DMN extraction

All the data were mainly preprocessed with the spm8 (<http://www.fil.ion.ucl.ac.uk/spm/>, Wellcome Department of Cognitive Neurology, UK). This included slice timing, head motion correction, spatial normalization, smoothing, filtering and the linear trend removal. No subject was excluded because all the head motion during scanning was less than 2 mm or  $2^\circ$ .

To define the regions of interest (ROIs) of the DMN, a data-driven method was employed: the group independent component analysis (GIFT, <http://www.icatb.sourceforge.net/>) (Calhoun et al., 2001). The optimal number of components was set to 20, which was calculated using the GIFT dimensionality estimation tool. Firstly, data from each subject were reduced using principal component analysis (PCA), according to the selected number of components. Then the data were separated by independent component analysis (ICA) using the Extended Infomax algorithm. After that, spatial maps and time courses for each subject were back-reconstructed, and the spatial maps for each subject were entered into a one-sample t-test to identify voxels with activities that were significantly different from zero. The threshold for significance was set using a false discovery rate correction (FDR procedure,  $P<0.001$ , cluster extent of 80voxels). The spatial patterns that best matched the DMN template developed by Stanford University (Shirer et al., 2012) was selected. The selected DMN networks must have the largest spatial correlations with the templates and with correlation values at least double that of all other networks. Finally 13 clusters (or nodes) were identified in the DMN, and they became the entry for the following modular analysis. The same procedure described above was applied to extract the DAN and resulted in 9 clusters (or nodes).

### 5.5. Grand averaged modularity of DMN

The 22 regions in the DMN and the DAN were spherical regions of interest (ROIs, diameter 10 mm). The time courses of these ROIs were extracted from the data after smoothing (Bassett et al., 2011). The Pearson correlation coefficients were calculated for each pair of 22 regions to measure the functional connectivity between the given pair of regions, and then a  $22 \times 22$  correlation matrix was obtained for each subject in both the NS and SD sessions. The correlation matrix was further grand averaged across subjects in each session, and two weighted graphs (one for the NS session and another for the SD session) were obtained.

We then used BCT (brain connectivity toolbox) (<http://www.brain-connectivity-toolbox.net>), a widespread measurement introduced by Sporns to explore SD's effects on the modularization of brain networks. The procedure for the network measures followed their recently published paper (Rubinov and Sporns, 2010). The modular structure was compared between the NS session and the SD session, and the only altered structure was observed in the DMN, where one module in the NS session was split into two modules in the SD session. The DMN specific modular alteration at the group level may add insight into the module structure of the DMN in individuals.



### 5.6. Individual module number of DMN (mnDMN)

To further investigate the functional segmentation of the DMN in single subjects,  $13 \times 13$  correlation matrices between pairs of DMN regions in each subject was input into modular analysis. A community structure was obtained for each subject in each session. Modularity captures an important organizational principle critical to biological systems: integration within sub-systems allows efficient local processing, while sparse connections between sub-systems reduce the propagation of noise (Rubinov and Sporns, 2010). As modularity represents evolutionary and developmental optimization of multiple or changing selection criteria (Meunier et al., 2009), a modular network can evolve or grow into more modules and may vary across subjects under some specific conditions like sleep deprivation. So only the number of modules was considered in this study to estimate the SD related effects on the default mode network. We define this subject-specific number of DMN module as mnDMN. We presumed the mnDMN may reflect the diversity of the DMN, which may vary among subjects.

### 5.7. Statistical and correlation analysis

For the grand averaged DMN, we computed the correlation coefficient between the two subsystems of the DMN, and then used a paired t-test to explore the functional connectivity difference between the NS and the SD session. Furthermore, Pearson correlation coefficients were utilized to investigate whether individual differences in functional connectivity changes were related to individual differences in sleepiness and mood state.

For each participant, the number of DMN modules (mnDMN) was obtained both in the NS session and the SD session. Pearson correlation coefficients were used to explore whether the mnDMN was related to individual differences in rating scores of emotive pictures. The age and gender were included as covariates before Pearson correlation analysis to obtain comparable results.

### Disclosure statement

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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### REFERENCES

- Addis, D.R., Wong, A.T., Schacter, D.L., 2007. Remembering the past and imagining the future: Common and distinct neural substrates during event construction and elaboration. *Neuropsychologia* 45, 1363–1377.
- Alex Fornito, B.J.H., Zalesky, Andrew, Simons, Jon S., 2012. Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. *Proc. Natl. Acad. Sci. USA* 109, 12788–12793.
- Andrews-Hanna, J.R., Snyder, A.Z., Vincent, J.L., Lustig, C., Head, D., Raichle, M.E., Buckner, R.L., 2007. Disruption of large-scale brain systems in advanced aging. *Neuron* 56, 924–935.
- Andrews-Hanna, J.R., Reidler, J.S., Sepulcre, J., Poulin, R., Buckner, R.L., 2010. Functional-anatomic fractionation of the brain's default network. *Neuron* 65, 550–562.
- Bassett, D.S., Wymbs, N.F., Porter, M.A., Mucha, P.J., Carlson, J.M., Grafton, S.T., 2011. Dynamic reconfiguration of human brain networks during learning. *Proc. Natl. Acad. Sci. USA* 108, 7641–7646.
- Benca, R.M., Obermeyer, W.H., Thisted, R.A., Gillin, J.C., 1992. Sleep and psychiatric disorders: a meta-analysis. *Arch. Gen. Psychiatry* 49, 651.
- Broyd, S.J., Demanuele, C., Debener, S., Helps, S.K., James, C.J., Sonuga-Barke, E.J., 2009. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav. Rev.* 33, 279–296.
- Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 1124, 1–38.
- Calhoun, V.D., Adali, T., Pearson, G.D., Pekar, J.J., 2001. A method for making group inferences from functional MRI data using independent component analysis. *Hum. Brain Mapp.* 14, 140–151.
- Castellanos, F.X., Margulies, D.S., Kelly, C., Uddin, L.Q., Ghaffari, M., Kirsch, A., Shaw, D., Shehzad, Z., Di Martino, A., Biswal, B., Sonuga-Barke, E.J., Rotrosen, J., Adler, L.A., Milham, M.P., 2008. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 63, 332–337.
- Chen, Z.J., He, Y., Rosa-Neto, P., Germann, J., Evans, A.C., 2008. Revealing modular architecture of human brain structural networks by using cortical thickness from MRI. *Cereb. Cortex* 18, 2374–2381.
- De Havas, J.A., Parimal, S., Soon, C.S., Chee, M.W., 2012. Sleep deprivation reduces default mode network connectivity and anti-correlation during rest and task performance. *Neuroimage* 59, 1745–1751.
- Eichele, T., Debener, S., Calhoun, V.D., Specht, K., Engel, A.K., Hugdahl, K., von Cramon, D.Y., Ullsperger, M., 2008. Prediction of human errors by maladaptive changes in event-related brain networks. *Proc. Natl. Acad. Sci. USA* 105, 6173–6178.
- Filippini, N., MacIntosh, B.J., Hough, M.G., Goodwin, G.M., Frisoni, G. B., Smith, S.M., Matthews, P.M., Beckmann, C.F., Mackay, C.E., 2009. Distinct patterns of brain activity in young carriers of the APOE-ε4 allele. *Proc. Natl. Acad. Sci. USA* 106, 7209–7214.
- Girvan, M., Newman, M.E., 2002. Community structure in social and biological networks. *Proc. Natl. Acad. Sci. USA* 99, 7821–7826.
- Goldstein, A.N., Greer, S.M., Saletin, J.M., Harvey, A.G., Nitschke, J.B., Walker, M.P., 2013. Tired and apprehensive: anxiety amplifies the impact of sleep loss on aversive brain anticipation. *J. Neurosci.* 33, 10607–10615.
- Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc. Natl. Acad. Sci. USA* 100, 253–258.
- Gujar, N., Yoo, S.S., Hu, P., Walker, M.P., 2010. The unrested resting brain: sleep deprivation alters activity within the default-mode network. *J. Cognit. Neurosci.* 22, 1637–1648.
- Gujar, N., Yoo, S.S., Hu, P., Walker, M.P., 2011. Sleep deprivation amplifies reactivity of brain reward networks, biasing the

- appraisal of positive emotional experiences. *J. Neurosci.* 31, 4466–4474.
- Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C.F., Menon, V., Greicius, M.D., 2009. Distinct cerebellar contributions to intrinsic connectivity networks. *J. Neurosci.* 29, 8586–8594.
- Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., Sporns, O., 2008. Mapping the structural core of human cerebral cortex. *PLoS Biol.* 6, e159.
- Harrison, B.J., Pujol, J., López-Solà, M., Hernández, R.R., Deus, J., Ortiz, H., Soriano, M.C., Yücel, M., Pantelis, C., Cardoner, N., 2008. Consistency and functional specialization in the default mode brain network. *Proc. Natl. Acad. Sci. USA* 105, 9781–9786.
- Hayes, S.M., Salat, D.H., Verfaellie, M., 2012. Default Network Connectivity in Medial Temporal Lobe Amnesia. *J. Neurosci.* 32, 14622–14629a.
- He, Y., Wang, J., Wang, L., Chen, Z.J., Yan, C., Yang, H., Tang, H., Zhu, C., Gong, Q., Zang, Y., 2009. Uncovering intrinsic modular organization of spontaneous brain activity in humans. *PLoS One* 4, e5226.
- Hoddes, E., Dement, W., Zarcone, V., 1972. The development and use of the Stanford Sleepiness Scale (SSS). *Psychophysiology* 9, 431–436.
- Horowitz, S.G., Braun, A.R., Carr, W.S., Picchioni, D., Balkin, T.J., Fukunaga, M., Duyn, J.H., 2009. Decoupling of the brain's default mode network during deep sleep. *Proc. Natl. Acad. Sci. USA* 106, 11376–11378.
- Kahn-Greene, E.T., Lipizzi, E.L., Conrad, A.K., Kamimori, G.H., Killgore, W.D.S., 2006. Sleep deprivation adversely affects interpersonal responses to frustration. *Pers. Individ. Differ.* 41, 1433–1443.
- Kim, H., 2012. A dual-subsystem model of the brain's default network: self-referential processing, memory retrieval processes, and autobiographical memory retrieval. *Neuroimage* 61, 966–977.
- Laird, A.R., Eickhoff, S.B., Li, K., Robin, D.A., Glahn, D.C., Fox, P.T., 2009. Investigating the functional heterogeneity of the default mode network using coordinate-based meta-analytic modeling. *J. Neurosci.* 29, 14496–14505.
- Leech, R., Sharp, D.J., 2013. The role of the posterior cingulate cortex in cognition and disease. *Brain* 137, 12–32.
- Lei, X., Zhao, Z., Chen, H., 2013. Extraversion is encoded by scale-free dynamics of default mode network. *Neuroimage* 74, 52–57.
- Lei, X., Wang, Y., Yuan, H., Mantini, D., 2014. Neuronal oscillations and functional interactions between resting state networks. *Hum. Brain Mapp.* 35, 3517–3528.
- Liang, X., Zou, Q., He, Y., Yang, Y., 2013. Coupling of functional connectivity and regional cerebral blood flow reveals a physiological basis for network hubs of the human brain. *Proc. Natl. Acad. Sci. USA* 110, 1929–1934.
- Meunier, D., Achard, S., Morcom, A., Bullmore, E., 2009. Age-related changes in modular organization of human brain functional networks. *Neuroimage* 44, 715–723.
- Murphy, K., Birn, R.M., Handwerker, D.A., Jones, T.B., Bandettini, P. A., 2009. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced?. *Neuroimage* 44, 893–905.
- Nair, A., Keown, C.L., Datko, M., Shih, P., Keehn, B., Müller, R.A., 2014. Impact of methodological variables on functional connectivity findings in Autism Spectrum Disorders. *Hum. Brain Mapp.* 35, 4035–4048.
- Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. *Proc. Natl. Acad. Sci. USA* 98, 676–682.
- Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage* 52, 1059–1069.
- Salomon, R., Levy, D.R., Malach, R., 2013. Deconstructing the default: cortical subdivision of the default mode/intrinsic system during self-related processing. *Hum. Brain Mapp.*
- Sheline, Y.I., Barch, D.M., Price, J.L., Rundle, M.M., Vaishnavi, S.N., Snyder, A.Z., Mintun, M.A., Wang, S., Coalson, R.S., Raichle, M. E., 2009. The default mode network and self-referential processes in depression. *Proc. Natl. Acad. Sci. USA* 106, 1942–1947.
- Shirer, W.R., Ryali, S., Rykhlevskaia, E., Menon, V., Greicius, M.D., 2012. Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cereb. Cortex.* 22, 158–165.
- Sporns, O., 2013. Network attributes for segregation and integration in the human brain. *Curr. Opin. Neurobiol.* 23, 162–171.
- Stevens, A.A., Tappin, S.C., Garg, A., Fair, D.A., 2012. Functional brain network modularity captures inter- and intra-individual variation in working memory capacity. *PLoS One* 7, e30468.
- Tagliazucchi, E., von Wegner, F., Morzelewski, A., Brodbeck, V., Borisov, S., Jahnke, K., Laufs, H., 2013. Large-scale brain functional modularity is reflected in slow electroencephalographic rhythms across the human non-rapid eye movement sleep cycle. *Neuroimage* 70, 327–339.
- van der Helm, E., Yao, J., Dutt, S., Rao, V., Saletin, J.M., Walker, M. P., 2011. REM sleep depotentiates amygdala activity to previous emotional experiences. *Curr. Biol.* 21, 2029–2032.
- Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J. Pers. Soc. Psychol.* 54, 1063.
- Zhang, D., Raichle, M.E., 2010. Disease and the brain's dark energy. *Nat Rev Neurol* 6, 15–28.
- Zohar, D., Tzischinsky, O., Epstein, R., Lavie, P., 2005. The effects of sleep loss on medical residents' emotional reactions to work events: a cognitive-energy model. *Sleep: J. Sleep Sleep Disord. Res* 28, 47–54.